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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/664,326
Filing Date: September 18, 2000
Appellant(s): HABERMANN ET AL.

Carlos M. Tellez, Reg. No. 48,638
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed February 15, 2007 appealing from the Office action mailed May 30, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

No amendment after final has been filed.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

No evidence is relied upon by the examiner in the rejection of the claims under appeal.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim limitation that "the *E. coli* bacteria are not *E. coli* secretor mutants", added in the Amendment filed 7/15/05, is considered new matter. The claims are drawn to a process for selecting a signal peptide for secretory expression of hirudin or hirudin derivatives. The art at the time of filing had used only secretor mutants in hirudin or hirudin derivative expression. Therefore, since secretory expression of the product is required by the claim and since those of skill in the art had not previously used a non-secretor strain to express hirudin or its derivatives, using a non-secretion *E. coli* strain would have been counterintuitive. The present Application does not provide literal support or suggest using a non-secretor strain in the claimed method. The present Specification does not refer to the subgenus of "*E. coli* that are not secretor mutants". The closest the Specification comes to discussing secretion is the single mention of using "*E. coli* strain Mc1061, or the secretor mutant WCM100" in an example. In this

passage, Mc1061 was not identified as an *E. coli* strain that was not a secretor strain and there is nothing in the Specification to suggest that it is. One would need to look up the characteristics of that strain to know whether or not it was a non-secreting strain. In the example that mentions *E. coli* Mc1061, the Specification does not indicate which *E. coli* strain (Mc1061 or WCM100) was used in the tests and which gave the expression that was 1.5 times better than the comparative test (Ala-hirudin expression using WCM100/pCM7053); page 9, lines 23-24, page 10, lines 18-20, and page 11, lines 19-20 all again refer to expression of hirudin with different signal peptides as compared to Ala-hirudin expression using the *E. coli* strain WCM100/pCM7053). The object of the present Invention is to find a signal sequence that, when combined with Leu-hirudin, will permit direct processing to Leu-hirudin and subsequent *secretion* of native Leu-hirudin in optimal yields in *E. coli* in general (see for example p. 2, lines 19-24 and page 3, lines 1-2 which states that in order to find advantageous signal sequences). Therefore, the Specification does not suggest using a non-secretor strain of *E. coli* and there would be no obvious reason to do so, especially given that the claim requires *secretory* expression. While the Specification does support using the species, *E. coli* strain, Mc1061, which was disclosed in the Specification, it does not support the exclusion of the subgenus of *E. coli* secretion mutants.

(10) Response to Argument

Lack of discussion of non-secretor strains of E. coli is partial evidence of new matter in the present case.

Appellants argue that whether or not the specification teaches that "non secretor mutants should be used" is immaterial to the Appellants possession of the claimed subject matter. The examiner respectfully disagrees. In the determination of whether or not Appellants had possession of the claimed method, the examiner not only looked for literal support of using non-secretor *E. coli* strains, but also looked throughout the Specification for any suggestions that Appellant contemplated using the subgenus of *E. coli* that are not secretor mutants. The fact that the claims require secretory expression and the specification fails to disclose using *E. coli* that are not secretor mutants (the specification refers to strain Mc1061 one time but does not provide any indication that this is not a secretor mutant) or to discuss anything about using a secretor mutant versus a non-secretor strain supports the examiner's position that the Specification as filed does not support the limitation of using *E. coli* bacteria that are not secretor mutants.

Facts of present case different from *In re Johnson*

Mc 1061 would not be recognizable as being a non-secretor strain when reading the present Specification and it is not clear that it is used in the presently claimed method.

Appellants argue that because the *E. coli* strain Mc1061 is not a secretor mutant, Appellants were in possession of the methods instantly claimed. This argument has been considered but is not deemed persuasive for the following reasons. While the specification mentions the specific *E. coli* strain Mc1061, the specification does not mention that it was a non-secretion strain and does not indicate which *E. coli* strain (Mc1061 or WCM100) was used in the disclosed tests and which gave the expression

that was 1.5 times better than the comparative test (Ala-hirudin expression using WCM100/pCM7053); page 9, lines 23-24, page 10, lines 18-20, and page 11, lines 19-20 all again refer to expression of hirudin with different signal peptides as compared to Ala-hirudin expression using the E. coli strain WCM100/pCM7053.

Unlike In re Johnson, the present case does not disclose numerous species.

Contrary to Appellants assertion that "each of the genus-excluding provisos in *Johnson* was based on the disclosure of a single compound", in *In re Johnson*:

> Fifty specific choices are mentioned for the E precursor compound, a broad *class* is identified as embracing suitable choices for the E' precursor compound, and twenty-six examples are disclosed which detail fifteen species of polyarylene polyethers. Only fourteen of those species and twenty-three of the "examples" are within the scope of the claims now on appeal. Two *of the many choices* for E and E' precursor compounds are deleted from the protection sought, because appellant is claiming less than the full scope of his disclosure (emphasis added, *In re Johnson*, 194 USPQ 187, 195 (CCPA 1977).

In contrast, the present case has only one species or choice and this species (Mc 1061) is not indicated as being a non-secretor mutant and would not be recognized specifically as a non-secretor mutant by the skilled artisan. Moreover, there is no broad class identified as embracing a suitable *E. coli* subgenus, there are no examples of using the claimed subgenus or the single species described in the Specification, and instead of two choices being deleted, the present claims attempt to delete many undisclosed species from protection. In fact, *In re Johnson*, states, "appellants' grandparent application contains a broad and complete generic disclosure, coupled with *extensive examples fully supportive of the limited genus now claimed*" (*In re Johnson*, 194 USPQ 187, 196 (CCPA 1977), emphasis added). Therefore, while the specification may

provide support for using the *E. coli* strain Mc1061 in the claimed method, it does not support using a genus of *E. coli strains* that are not secretor mutants.

The present claims have excluded the use of secretor mutants. This limitation is equivalent to the positive limitation that only non-secretor strains of E. coli can be used. Thus, the examiner has looked to the Specification for a disclosure of using only non-secretor strains. Unlike In re Johnson, the present case does not have many examples which meet the limitations of the claims. In fact, the present case does not have any examples of a method which meets the limitations of the claims. The specification mentions one time that the strain Mc1061 was transformed on ampicillin resistant plates but does not identify it as a non-secretor and there is no evidence in the Specification that it is a non-secretor. Thus, in an art that only has experience using secretor mutants to express hirudin derivatives in E. coli and in light of the claims that require secretory expression, it would not be clear to the skilled artisan that Appellant was in possession of using non-secretor strains.

Unlike In re Johnson, species excluded is not equivalent to species remaining

Appellants argue that the Specification provides examples of using a secretor mutant in the claimed method and that "[I]f alternative elements are positively recited in the specification, they may be explicitly excluded in the claims." (citing MPEP 2173.05(i) and *In re Johnson*, 558 F.2d 1008, 1019 194 USPQ 187, 196 (CCPA 1977). This argument has been considered but is not deemed persuasive because unlike *In re Johnson* where the excluded species were equivalent to the species allowed in the claims, in the present case which is drawn to a method of expression that requires

secretion, it is unclear that non-secretor mutants and secretor mutants would function equivalently. The Specification and the art do not provide any guidance or evidence that non-secretor strains would work as well as secretor mutants in the present invention. In fact, it is likely that non-secretor mutants could not be used successfully in the claimed method because only a limited and unmeasurable amount of protein could be secreted. Thus, one of skill in the art would not readily recognize that Appellants were in possession of the claimed invention at the time of filing.

Unlike In re Johnson, one of skill in the art would not recognize from the Specification that the method could be practiced with a non-secretor strain

The present Specification does not disclose practicing the method using only non-secretor strains. In addition, the art only taught the expression of hirudin derivatives in *E. coli* using secretor mutants. Thus, reading the present Specification would not suggest to one of skill in the art that practicing the claimed method of identifying signal peptides in hirudin expression in non-secretor strains of *E. coli* was contemplated at the time of filing the present application.

Unlike In re Johnson, there is no example of practicing a method that meets the limitations of the claims

Appellants argue that similar to *In re Johnson*, the proviso of claim 6 excludes secretor mutants, one example of which is taught in the specification. Appellants cited the following passage from *In re Johnson*,

> [t]he notion that one who fully discloses and teaches those skilled in the art how to make and use a genus and *numerous species there within*, has somehow failed to disclose, and teach those skilled in the art how to make and use, that genus minus two of those species, and has thus failed to satisfy the requirements of §112, first paragraph, appears to result in hypertechnical application of legalistic prose relating to that provision of

> the statute. (emphasis added, *In re Johnson*, 194 USPQ 187, 196 (CCPA 1977).

However, unlike *In re Johnson*, the present case does not teach how to make and use *numerous species* within the genus. As explained above, In *In re Johnson*, there were 50 specific choices for E precursor and a broad class identified as embracing suitable choices for E'. In addition, there were twenty-three examples of different species which met the limitation of the claims. In the present case, there is not a single example in the Specification that would meet the limitation of the claims and the art also did not provide any examples of hirudin expression in E. coli using non-secretor strains. Thus, it would not be apparent to the skilled artisan, in reading the present Specification, that such a method limited to using only non-secretor *E. coli* strains was contemplated at the time of filing the Application.

Present claims do not positively recite a single species that represents an obvious class (genus) of compounds

Appellants argue that *In re Herschler*, 591, F.2d 693, 701 (CCPA 1979) found that a single example disclosing a single corticosteroid in the solvent DMSO was sufficient written description support of a method of enhancing dermal penetration of a genus of "physiologically active steroid[s]" and that the court did not require the inventor to be in possession of all possible physiologically active steroids that could be used in the method. Appellants use inquiry that they contend is similar to that used in *In re Herschler*, asking "would the worker of ordinary skill in this art consider *E. coli* that are not secretor mutants to be operative in a process for selecting a signal peptide for secretory expression of a protein in *E. coli* when considering the application disclosure?

This argument and discussion has been considered but is not deemed persuasive. In *In re Herschler*, the species used in the example in the Specification was dexamethasone 21-phosphate which was known to be in a class of corticosteroids which were known subgenus of steroids. It was very well known in the art that steroids have similar chemical structures and consequently similar chemical properties. Thus, due to their similar chemical structures, those of skill in the art would know that if one steroid had the chemical property of being able to penetrate the skin aided by DMSO then the others in the class could as well. In contrast, non-secretor *E. coli* strains have not been used to express hirudin derivatives. The prior art only discloses expression of hirudin derivatives in secretor mutants and teaches that such secretor mutants allow for high production of the hirudin derivative in the growth medium (secreted). Moreover, the present claims are drawn to a process of selecting a signal peptide for *secretory* expression, therefore secretion is required in the present claims. Thus, unlike *In re Herschler*, it would not have been known by or obvious to the skilled artisan whether or not non-secretor strains could be used to successfully practice a method of selecting signal peptides for secretory expression of a desired hirudin or hirudin derivative as claimed. Secretor mutants were known to express high amounts of hirudin derivatives in the culture supernatant (see Office Action mailed , p. 10, 1st and 2nd paragraphs). Since non-secretor strains had never been used in hirudin derivative expression, it would not have been known whether or not the use of non-secretor strains would affect the ability of the signal peptides to secrete enough of the hirudin derivative in the culture supernatant so that it could be measured. This was unknown in the art and was not

discussed in the present Specification. In other words, unlike *In re Herschler*, the species (secretor or non-secretor) in the present case are not known equivalents in the genus (*E. coli*).

Secretion is essential to presently claimed method therefore the choice of secretor or non-secretor is possibly essential.

Appellants argue that the present situation is analogous to Example 18 of the USPTO training materials because the use of non-secretor strains of *E. coli* is not essential to the claimed method. This argument has been considered but is not deemed persuasive. In Example 18, the specification teaches a method for producing proteins using mitochondria from the fungus *Neurospora crassa*. The Specification in the example teaches that the mitochondria is essential and it is known that the nucleic acid is not essential. Thus, a single example in the specification of β-galactosidase expression using mitochondria from *Neurospora crassa* was sufficient to meet the written description requirements because it was known that the nucleic acid sequence was not essential to the invention. In contrast, the present invention is drawn to a process for selecting a signal peptide for *secretory* expression of hirudin and therefore secretion is essential. The art only teaches expression of hirudin in secretion mutants and that using such a system allows for expression and secretion of massive amounts of protein into the culture (see Office Action mailed 1/7/03, p. 9, last few lines). The Specification mentions strain Mc1061, but does not teach whether it could be used successfully in the claimed method. Therefore, one of skill in the art would not know how using a non-secretor strain of *E. coli* would affect the secretion of hirudin in the

claimed assay and would not know whether or not this particular sub-genus *E. coli* was essential.

In the present case, one of skill in the art would not be able to recognize that Appellants were in possession of a method of selecting a signal peptide for secretory expression of a desired hirudin or hirudin derivative protein *E. coli* wherein the *E. coli* is not a secretor mutant (or in other words, using a non-secretor strain of *E. coli*) for the reasons explained above.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Holly G. Schnizer

Conferees:

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